Ruoff (#1284)						
Kalamazoo, MI	2	2 (100%)	2	2 (100%)	3	2 (67%)
Sachs (#14126)						
Stamford, CT	2	1 (50%)	1	1 (100%)	2	2 (100%)
Schaffer (#11394)						
Conyers, GA	1	1 (100%)	0	-	1	1 (100%)
Schmidt (#13421)						
Philadelphia, PA	1	0 (0%)	1	1 (100%)	2	2 (100%)
Scholar (#13422)						
Walla Walla, WA	4	2 (50%)	4	2 (50%)	3	2 (67%)
Simon (#9773)						
Austell, GA	19	15 (79%)	21	14 (67%)	20	15 (75%)
Smith (#14148)						
Albany, NY	1	1 (100%)	1	1 (100%)	1	0 (0%)
Sprague (#13492)						
Augusta, GA	1	1 (100%)	1	0 (0%)	1	1 (100%)
Stein (#13423)						
Manchester, CT	1	0 (0%)	1	0 (0%)	0	-
Stewart (#13670)						
Las Vegas, NV	2	2 (100%)	2	0 (0%)	2	2 (100%)
Thwainey (#13424)						
Dearborn, MI	0	-	0	-	1	0 (0%)
Tidman (#11281)						
Blue Ridge, GA	7	5 (71%)	6	3 (50%)	6	4 (67%)
Tonkens (#13672)						
Henderson, NV	1	1 (100%)	1	1 (100%)	1	1 (100%)
Tucker (#4996)						
Wenatchee, WA	1	1 (100%)	1	1 (100%)	2	2 (100%)
Ulrich (#13426)						
Zanesville, OH	4	2 (50%)	3	2 (67%)	4	3 (75%)
Upchurch (#13008)						
Birmingham, AL	11	6 (55%)	11	7 (64%)	11	10 (91%)
Warren (#13130)						
Memphis, TN	2	1 (50%)	1	1 (100%)	2	1 (50%)
Weissberger (#13419)						
Atlantis, FL	1	0 (0%)	2	1 (50%)	2	2 (100%)
Williams, II (#13039)						
Trenton, TN	4	3 (75%)	3	1 (33%)	3	2 (67%)
Wong (#2848)						
Lafayette, LA	7	4 (57%)	8	5 (63%)	8	6 (75%)
Yarbrough (#11638)						
Gainesville, GA	1	1 (100)	2	2 (100%)	1	1 (100%)
Ziporin (#13420)						
Denver, CO	1	0 (0%)	0	-	1	1 (100%)
TOTAL	**297**	**213**	**302**	**210**	**304**	**223**
[redacted]						
[redacted]						

@CDTR-PI = cefditoren pivoxil
+CLA = clarithromycin
! "Enrolled" patients are equivalent to ITT patients in this study
^ Clinically Evaluable at Follow-Up Visit as per Applicant ISE data set

MO Comment: ***DSI has confirmed that the information from the DeAbate and Mathew sites should be considered unreliable and that its exclusion from analyses is appropriate. Further details regarding the Applicant's reasons for excluding these sites can be found in the NDA 21,222 Amendment 016 Volume 1 of 1, June 13, 2000 submission.***

It is notable that 20 of the remaining sites were also used as study sites in the previously reviewed AECB pivotal study. These 20 sites enrolled 460/903 (51%) patients in this study.

****

DATA PRESENTED, BY THE APPLICANT AND THE MO, FROM THIS POINT FORWARD WILL EXCLUDE PATIENTS FROM THE DEABATE AND MATHEW SITES

****

Of the 903 patients included in the Applicant's ITT analysis, 646 (213 in the CDTR-PI 200 mg group, 210 in the CDTR-PI 400 mg group, and 223 in the CLA group) patients were considered clinically evaluable at the Follow-Up visit. Of the 646 patients who were clinically evaluable, 52 patients (15 in the CDTR-PI 200 mg group, 15 in the CDTR-PI 400 mg group and 22 in the CLA group) were clinically "evaluable with variation" (50 had a mistimed visit, 1 had admission criteria not met, and 1 had received another antimicrobial agent pretreatment). Of the 257 patients who were not evaluable, 199 patients (66, 72, and 61 in the CDTR-PI 200 mg, CDTR-PI 400 mg, and CLA groups, respectively) did not have a causative respiratory pathogen isolated pretreatment, 29 patients did not have a clinical response assessed within the specified visit window, 6 patients were previously enrolled in a cefditoren study with the same indication, 5 patients received less than 3 consecutive days of study drug, 4 patients were misdiagnosed, 3 patients received less than 80% of study drug, 10 patients received additional antimicrobials, and 1 patient was lost to follow-up.

Of the 903 patients included in the Applicant's ITT analysis, 647 patients (215 in the CDTR-PI 200 mg group, 210 in the CDTR-PI 400 mg group, and 222 in the CLA group) were considered microbiologically evaluable at the Follow-Up visit. Of the 647 patients who were microbiologically evaluable, 176 patients were microbiologically "evaluable with variation" (140 with pre-therapy gram stain at central lab not adequate, 1 that received an additional antimicrobial agent pretreatment, and 49 with missed timing of visit). Reasons for microbiologic unevaluability were the same as for clinical unevaluability with two exceptions: rather than 29

patients not having a clinical response assessment within the visit window, 31 patients did not have a culture obtained within the visit window, one less patient in the CDTR-PI 200 mg arm and one less patient in the CLA arm are is listed as having "received additional antimicrobials," and one less patient in the CDTR-PI 400 mg arm "received less than 80% of study drug."

The disposition of patients according to the Applicant is presented in Table 34. (Table 11.1a., Volume 217 of 322, page 064)

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Table 34. Disposition of Patients According to the Applicant

Table 11.1a. Disposition of Patients by Data Set

	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CLA 500 mg BID
All Patients: Randomized and Received Study Drug[a]	**297**	**302**	**304**
Included in Clinically Evaluable Efficacy Analyses:			
Post-Therapy	209	199	218
Follow-Up	213	210	223
Excluded at Post-Therapy:	**88**	**103**	**86**
No target pathogen isolated pretreatment	66	72	61
No clinical response assessed within visit window	15	25	18
Previously enrolled in a study with the same indication	3	0	3
Received less than 3 consecutive days of study drug	0	3	2
Misdiagnosis	3	0	1
Received less than 80% of study drug	0	2	1
Lost to follow-up	1	0	0
Received additional antimicrobials	0	1	0
Excluded at Follow-Up:	**84**	**92**	**81**
No target pathogen isolated pretreatment	66	72	61
No clinical response assessed within visit window	10	12	7
Received additional antimicrobials	1	3	6
Previously enrolled in a study with the same indication	3	0	3
Received less than 3 consecutive days of study drug	0	3	2
Misdiagnosis	3	0	1
Received less than 80% of study drug	0	2	1
Lost to follow-up	1	0	0
Included in Microbiologically Evaluable Efficacy Analyses:			
Post-Therapy	208	198	217
Follow-Up	215	210	222
Excluded at Post-Therapy:	**89**	**104**	**87**
No target pathogen isolated pretreatment	66	72	61
No culture obtained within visit window	14	23	18
Received less than 3 consecutive days of study drug	1	4	2
Received less than 80% of study drug	1	4	2
Previously enrolled in a study with the same indication	3	0	3
Misdiagnosis	3	0	1
Lost to follow-up	1	0	0
Received additional antimicrobials	0	1	0
Excluded at Follow-Up:	**82**	**92**	**82**
No target pathogen isolated pretreatment	66	72	61
No culture obtained within visit window	8	14	9
Received additional antimicrobials	1	2	5
Previously enrolled in a study with the same indication	3	0	3
Received less than 3 consecutive days of study drug	0	3	2
Misdiagnosis	3	0	1
Received less than 80% of study drug	0	1	1
Lost to follow-up	1	0	0

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin

[a] All data from sites 4637 and 13004 were excluded; see Section 6.0

MO Comment: ***Four of the eight patients who received additional antimicrobials received them for infections related to the upper respiratory tract [redacted] Signs and symptoms of sinusitis may***

be similar to those found in AECB. Therefore, unless these patients showed improvement or clearance of all signs and symptoms used to document their episode of AECB at the Follow-UP visit, they will be considered evaluable failures in MO analyses.

There were six more microbiologically evaluable patients than there were clinically evaluable patients (3 in the CDTR-PI 200 mg group, 2 in the CDTR-PI 400 mg group, and 1 in the CLA group) in the Applicant's Follow-Up microbiologic analyses (based on review of the Applicant's SAS data set). Since the Applicant requires a patient to be clinically evaluable to be microbiologically evaluable, these six patients should not have been microbiologically evaluable and will not be considered evaluable in the MO analyses.

The Applicant's "all patient" data set is more correctly defined as the ITT data set since it included all patients enrolled who took at least one dose of study drug. The "ITT" data set is more correctly defined as the MITT data set since it also required that patients have at least one "causative respiratory pathogen" on the pretreatment sputum sample. Patients included in the Applicant's "ITT" data set were calculated from the Applicant's ISE data base by excluding patients who had negative pretreatment sputum cultures and these results are included in Table 35.

The MO has required that that the pretreatment culture have a protocol defined "causative respiratory pathogen" (per protocol target respiratory pathogens for this study were H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, S. pneumoniae, and S. pyogenes). The MO has also required that the gram stain at the central lab to be "good," and that the patient had at least two signs or symptoms consistent with AECB be included a patient in the MITT population. These requirements have resulted in a smaller MITT population and lower overall evaluability rate in the MO's analyses, as is seen in Table 35. Of note, the MO's evaluability rates of 45-51% are more consistent with the evaluability rate of 50% predicted by the Applicant in their determination of sample size calculation, than the evaluability rates of 70-73% in the Applicant's analyses.

Table 35. Disposition of Patients According to the Clinical Reviewer Compared to the Applicant

	@CDTR-PI 200 mg			@CDTR-PI 400 mg			+CLA 500 mg		
	Enrolled	MITT	*Eval (%)	Enrolled	MITT	*Eval (%)	Enrolled	MITT	*Eval (%)
TAP	297	231	213 (72%)	302	230	210 (70%)	304	243	223 (73%)
MO	297	165	146 (49%)	302	156	135 (45%)	304	173	154 (51%)

@CDTR-PI = cefditoren pivoxil
+CLA = clarithromycin
*Clinically evaluable at Test-of-Cure visit (see review text for TAP and MO criteria)

3.2.2.4.2 Demographics

3.2.2.4.2.1 General

The Applicant found no statistically significant differences between treatment groups for the demographic variables of gender, age, race, weight, or height for all patients or for clinically evaluable patients. In the clinically evaluable population, fourty-eight percent of the patients were males and 89% of the patients were Caucasian. The mean age of the clinically evaluable study population was 49.9 years and the median age 51 years (range from 13 to 89 years). A summary of demographic information for all patients by treatment group is presented in Table 36. (Table 11.2a., Volume 217 of 322, page 067) and for clinically evaluable patients by treatment group in Table 37. (modified from Table 14.1-3.2, Volume 218 of 322, pages 115-116).

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Table 36. Demographic Information for All Patients According to the Applicant

Table 11.2a. Demographic Information (All Patients)

Demographic Characteristic	Number of Patients by Treatment Group			P-value[a]
	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CLA 500 mg BID	
Total Treated	297	302	304	
Gender				0.722
Female	151 (51%)	163 (54%)	162 (53%)	
Male	146 (49%)	139 (46%)	142 (47%)	
Race[b]				0.404
Caucasian	263 (89%)	268 (89%)	279 (92%)	
Black	22 (7%)	22 (7%)	12 (4%)	
Hispanic	9 (3%)	10 (3%)	11 (4%)	
Other	3 (1%)	2 (1%)	2 (1%)	
Age (years)[c]				0.820
<45	116 (39%)	130 (43%)	118 (39%)	
45 - 65	119 (40%)	104 (34%)	110 (36%)	
>65	62 (21%)	68 (23%)	76 (25%)	
Mean (SD)	49.4 (16.9)	49.5 (17.3)	50.2 (17.6)	
Range	13 - 85	14 - 86	17 - 89	
Weight (pounds)[c]				0.347
<135	47 (16%)	57 (19%)	50 (16%)	
135 - 165	84 (28%)	93 (31%)	91 (30%)	
166 - 195	75 (25%)	67 (22%)	66 (22%)	
>195	91 (31%)	84 (28%)	96 (32%)	
Missing	0	1 (<1%)	1 (<1%)	
Mean (SD)	178.2 (46.5)	173.3 (45.0)	178.0 (49.0)	
Range	89 - 380	83 - 370	82 - 365	
Height (inches)[c]	N=296	N=301	N=304	0.860
Mean (SD)	67.0 (3.9)	66.8 (4.0)	66.8 (4.0)	
Range	54 - 76	56 - 77	53 - 79	

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; SD = standard deviation

[a] P-values are from Chi-square test (two-tailed) for gender and race, and a one-way analysis of variance using treatment as the factor for age, weight, and height.

[b] P-value from Chi-square test using Caucasian versus Black versus all other races combined.

[c] At baseline.

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Table 37. Demographic Information for Clinically Evaluable Patients According to the Applicant

Modified Table 14.1-3.2 Demographic Variables Evaluable Patients				
	Number of Patients by Treatment Group			
Demographic Characteristic	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CLA 500 mg BID	P-value[a]
Total Treated	213	210	223	
Gender				0.768
Female	116 (54%)	109 (52%)	114 (51%)	
Male	97 (46%)	101 (48%)	109 (49%)	
Race[b]				0.281
Caucasian	192 (90%)	182 (87%)	203 (91%)	
Black	16 (8%)	18 (9%)	10 (4%)	
Hispanic	4 (2%)	8 (4%)	8 (4%)	
Other	1 (<1%)	2 (1%)	2 (1%)	
Age (years)[c]				0.659
<45	85 (40%)	85 (40%)	83 (37%)	
45 - 65	84 (39%)	77 (37%)	82 (37%)	
>65	44 (21%)	48 (23%)	58 (26%)	
Mean (SD)	49.3 (17.0)	49.7 (17.7)	50.7 (17.5)	
Range	13 - 85	14 - 86	17 - 89	
Weight (pounds)[c]				0.420
<135	33 (15%)	41 (20%)	37 (17%)	
135 - 165	67 (31%)	67 (32%)	72 (32%)	
166 - 195	48 (23%)	45 (21%)	48 (22%)	
>195	65 (31%)	56 (27%)	65 (29%)	
Missing	0	1 (<1%)	1 (<1%)	
Mean (SD)	176.7 (46.0)	171.1 (42.6)	175.1 (47.5)	
Range	98- 380	83 - 350	91-348	
Height (inches)[c]	N=212	N=209	N=223	0.687
Mean (SD)	66.7 (3.9)	67.0 (4.1)	67.0 (3.9)	
Range	54 - 76	56 - 77	53 - 79	

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; SD = standard deviation

[a] P-values are from Chi-square test (two-tailed) for gender and race, and a one-way analysis of variance using treatment as the factor for age, weight, and height.

[b] P-value from Chi-square test using Caucasian versus Black versus all other races combined.

[c] At baseline.

Statisticial Reviewer's comments: ***The Applicant's Demographic data are described for all and clinically evaluable patients in Table 36 and Table 37 and no statistically significant differences were detected for gender, age, race, weight and height between the treatment groups. The MO's reclassification of data, for the evaluable population, did not result in any statistically significant difference for the demographic variables.***

3.2.2.4.2.2 Baseline Diagnosis and Disease Characteristics

The Applicant has also examined the treatment groups by baseline diagnosis and baseline disease characteristics. In the MITT and

clinically evaluable populations no statistically significant differences were observed. A summary of baseline diagnosis and disease characteristics for the Applicant's MITT population is provided in Table 38. (Volume 217 of 322, page 069, Table 11.2b) and for the clinically evaluable population in Table 39. (modified from September 13, 2000 submission, Volume 1 of 1, page 002, Table 14.1-4.2).

Table 38. Summary of Diagnoses and Baseline Characteristics for All Patients According to the Applicant

Diagnoses and Baseline Characteristics	Number of Patients by Treatment Group CDTR-PI 200 mg BID	 CDTR-PI 400 mg BID	 CLA 500 mg BID	P-value[a]
Total Treated	297	302	304	
Diagnosis				0.824
Chronic bronchitis	247 (83%)	249 (82%)	247 (81%)	
Asthmatic bronchitis	50 (17%)	53 (18%)	57 (19%)	
Number of LRTIs Within Past Year				0.363
1	70 (24%)	68 (23%)	76 (25%)	
2 - 4	192 (65%)	200 (66%)	206 (68%)	
>4	35 (12%)	34 (11%)	22 (7%)	
Infection Status				0.743
Mild	44 (15%)	41 (14%)	38 (13%)	
Moderate	247 (83%)	252 (83%)	261 (86%)	
Severe	6 (2%)	9 (3%)	5 (2%)	
Clinical Condition				0.803
Good	113 (38%)	107 (35%)	112 (37%)	
Fair	179 (60%)	190 (63%)	189 (62%)	
Poor	5 (2%)	5 (2%)	3 (1%)	
Smoking Status				0.199
Non-smoker	47 (16%)	52 (17%)	68 (22%)	
Smoker	147 (49%)	145 (48%)	148 (49%)	
Ex-smoker	103 (35%)	105 (35%)	88 (29%)	
Alcohol Use				0.330
Non-drinker	164 (55%)	148 (49%)	143 (47%)	
Drinker	112 (38%)	128 (42%)	137 (45%)	
Ex-drinker	21 (7%)	26 (9%)	24 (8%)	

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; LRTIs = lower respiratory tract infections

[a] P-values are from Chi-square test for diagnosis, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status, clinical condition, and number of LRTIs within the past year.

Table 39. Summary of Diagnoses and Baseline Characteristics for Clinically Evaluable Patients According to the Applicant

Modified Table 14.1-4.2. Baseline Characteristics Evaluable Patients				
	Number of Patients by Treatment Group			
Diagnoses and Baseline Characteristics	CDTR-PI 200 mg BID	CDTR-PI 400 mg BID	CLA 500 mg BID	P-value[a]
Total Treated	213	210	223	
Diagnosis				0.571
Chronic bronchitis	179 (84%)	174 (83%)	179 (80%)	
Asthmatic bronchitis	34 (16%)	36 (17%)	44 (20%)	
Number of LRTIs Within Past Year				0.232
1	51 (24%)	49 (23%)	51 (23%)	
2 - 4	134 (63%)	141 (67%)	157 (70%)	
>4	28 (13%)	20 (10%)	15 (7%)	
Infection Status				0.872
Mild	31 (15%)	26 (12%)	26 (12%)	
Moderate	177 (83%)	180 (86%)	195 (87%)	
Severe	5 (2%)	4 (2%)	2 (1%)	
Clinical Condition				0.617
Good	86 (40%)	77 (37%)	87 (39%)	
Fair	123 (58%)	128 (61%)	135 (61%)	
Poor	4 (2%)	5 (2%)	1 (<1%)	
Smoking Status				0.197
Non-smoker	29 (14%)	40 (19%)	47 (21%)	
Smoker	102 (48%)	97 (46%)	109 (49%)	
Ex-smoker	82 (38%)	73 (35%)	67 (30%)	
Alcohol Use				0.334
Non-drinker	115 (54%)	99 (47%)	102 (46%)	
Drinker	87 (41%)	95 (45%)	101 (45%)	
Ex-drinker	11 (5%)	16 (8%)	20 (9%)	

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; LRTIs = lower respiratory tract infections

[a] P-values are from Chi-square test for diagnosis, smoking status and alcohol use, and from Cochran-Mantel-Haenszel test for infection status, clinical condition, and number of LRTIs within the past year.

3.2.2.4.2.3 Pretreatment Signs and Symptoms

The Applicant also analyzed pretreatment signs and symptoms (sputum appearance, sputum volume, cough, dyspnea, fever, rales, rhonchi, wheeze, and cyanosis) in the MITT and clinically evaluable populations and found no statistically significant differences between treatment groups.

3.2.2.4.2.4 Concurrent Medications

According to the Applicant, 93% of the patients in the CDTR-PI 200 mg group, 94% of the patients in the CDTR-PI 400 mg group, and 95% of the patients in the CLA group used concurrent medications during the study. The high incidence of concurrent medications during the study resulted from use of medications generally administered for treatment of fevers, coughs, colds, and other symptoms associated with bronchitis, as well as the use of

oral contraceptives and hormone replacement therapy among female patients. A summary of concurrent medication use is provided in Table 40. (Volume 217 of 322, page 073, Table 11.2d).

Table 40. Summary of Commonly Used Concurrent Medications in All Patients According to the Applicant

Table 11.2d. Summary of Commonly Used Concurrent Medications (All Patients)

Therapeutic Subclassification	CDTR-PI 200 mg BID (N=297)	CDTR-PI 400 mg BID (N=302)	CLA 500 mg BID (N=304)
Anti-asthmatics (e.g., [redacted] theophylline, salmeterol xinafoate, Combivent)	153 (52%)	162 (54%)	162 (53%)
Analgesics (e.g., acetylsalicylic acid, [redacted] Vicodin, Medinite)	117 (39%)	120 (40%)	116 (38%)
Cough and cold preparations (e.g., guaifenesin, [redacted] Robitussin DM)	108 (36%)	103 (34%)	110 (36%)
Corticosteroids for systemic use (e.g., fluticasone propionate, prednisone, triamcinolone acetonide, beclomethasone dipropionate)	95 (32%)	111 (37%)	103 (34%)
Antibacterials for systemic use (e.g., azithromycin, levofloxacin, trovafloxacin [redacted] clarithromycin)	60 (20%)	67 (22%)	60 (20%)
Psychoanaleptics (e.g., fluoxetine HCl, sertraline HCl, [redacted]	60 (20%)	58 (19%)	64 (21%)
Sex hormones and modulators of the genital system (e.g., medroxyprogesterone acetate, Provella-14)	50 (17%)	58 (19%)	58 (19%)
Anti-inflammatory and antirheumatic products (e.g., ibuprofen, naproxen)	58 (20%)	41 (14%)	59 (19%)
Antacids, drugs for treatment of peptic ulcer and flatulence (e.g., omeprazole, ranitidine HCl, famotidine)	49 (16%)	52 (17%)	50 (16%)
Psycholeptics (e.g., [redacted] lorazepam, diazepam)	55 (19%)	50 (17%)	43 (14%)
Antihistamines for systemic use (e.g., loratadine, fexofenadine HCl)	40 (13%)	41 (14%)	44 (14%)
Diuretics (e.g., furosemide, dyazide)	41 (14%)	35 (12%)	44 (14%)
Nasal preparations (e.g., beclometasone dipropionate, Respaire-SR-120, pseudoephedrine HCl)	47 (16%)	32 (11%)	30 (10%)
Agents acting on the renin-angiotensin system (e.g., lisinopril, enalapril maleate)	28 (9%)	29 (10%)	36 (12%)
Mineral supplements (e.g., potassium chloride)	20 (7%)	31 (10%)	27 (9%)

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin

Twenty percent of the patients in the CDTR-PI 200 mg group, 22% of the patients in the CDTR-PI 400 mg group, and 20% of the patients in the CLA group reported use of other systemic antibacterials, which according to the Applicant were generally prescribed subsequent to failing treatment or at the end of the study.

Per the Applicant, of patients that were considered clinically evaluable, 1 patient in the CDTR-PI 400 mg group received additional antimicrobials for the current infection and was

considered an evaluable presumed clinical failure at the Post-Therapy Visit; 1 patient in the CDTR-PI 200 mg group, 4 patients in the CDTR-PI 400 mg group, and 2 patients in the CLA group, received additional antimicrobials for the current infection after the Post-Therapy Visit and were considered evaluable presumed clinical failures at the Follow-Up Visit.

3.2.2.4.2.5 Pretreatment Susceptibility Results

Susceptibility results were generally similar for the two study drugs with one exception, of 65 *S. pneumoniae* isolates, none were resistant to cefditoren (based on MICs proposed by the Applicant) and 13 were resistant to clarithromycin. Pretreatment susceptibilities to cefditoren pivoxil and clarithromycin for the target pathogens are presented in Table 41. (Volume 217 of 322, page 075, Table 11.2f.).

Table 41. Pretreatment Susceptibility Results for Target Pathogens According to the Applicant

Table 11.2f. Pretreatment Susceptibility Results for Target Pathogens

	Cefditoren Susceptibility				Clarithromycin Susceptibility				
Target Pathogen	**S**	**I**	**R**	**U**	**S**	**I**	**R**	**U**	**TOTAL**
H. parainfluenzae	463	1	0	11	316	103	45	11	475
H. influenzae	153	0	0	12	121	28	4	12	165
M. catarrhalis	105	0	0	0	105	0	0	0	105
S. pneumoniae	65	0	0	0	49	3	13	0	65
S. aureus	74	1	3	0	60	0	18	0	78
S. pyogenes	4	0	0	0	4	0	0	0	4

S = susceptible; I = intermediate; R = resistant; U = unknown
Susceptibility breakpoints:
Cefditoren: S = MIC ≤2 mcg/mL; I = MIC = 4 mcg/mL; R = MIC ≥8 mcg/Ml
Clarithromycin: S = MIC ≤2 mcg/mL; I = MIC = 4 mcg/mL; R = MIC ≥8 mcg/Ml
(*Haemophilus*): S = MIC ≤8 mcg/mL; I = MIC = 16 mcg/mL; R = MIC ≥32 mcg/Ml
(*S. pneumoniae, Beta Streptococci*): S = MIC ≤0.25 mcg/mL; I = MIC = 0.5 mcg/mL; R = MIC ≥ 1 mcg/mL

Susceptibility results were also assessed for selected pathogens by penicillinase production and oxacillin and/or penicillin resistance, these results are summarized in Table 42. (Volume 217 of 322, page 077, Table 11.2g.).

Table 42. Pretreatment Susceptibility Results for Selected Penicillinase-Producing, Oxacillin-Resistant, and/or Penicillin-Resistant Target Pathogens According to the Applicant

Table 11.2g. Pretreatment Susceptibility Results for Selected Penicillinase-Producing, Oxacillin-Resistant, and/or Penicillin-Resistant Target Pathogens

	Cefditoren Susceptibility				Clarithromycin Susceptibility				TOTAL
	S	I	R	U	S	I	R	U	
Penicillinase-Producing Pathogens									
H. influenzae	41	0	0	2	30	10	1	2	43
H. parainfluenzae	32	1	0	1	27	4	2	1	34
M. catarrhalis	92	0	0	0	92	0	0	0	92
S. aureus	70	1	2	0	56	0	17	0	73
Oxacillin-Resistant Pathogens									
S. aureus	0	1	3	0	1	0	3	0	4
Penicillin-Resistant Pathogens									
S. aureus	63	1	3	0	49	0	18	0	67
S. pneumoniae	9	0	0	0	4	0	5	0	9

S = susceptible; I = intermediate; R = resistant; U = unknown
Susceptibility breakpoints:
Cefditoren: S = MIC ≤2 mcg/mL; I = MIC = 4 mcg/mL; R = MIC ≥8 mcg/mL
Clarithromycin: S = MIC ≤2 mcg/mL; I = MIC = 4 mcg/mL; R = MIC ≥8 mcg/mL
(*Haemophilus*): S = MIC ≤8 mcg/mL; I = MIC = 16 mcg/mL; R = MIC ≥32 mcg/mL
(*S. pneumoniae, Beta Streptococci*): S = MIC ≤0.25 mcg/mL; I = MIC = 0.5 mcg/mL; R = MIC ≥ 1 mcg/mL

3.2.2.4.2.6 Treatment Compliance

According to the Applicant, there was no statistically significant difference in treatment duration or study drug compliance between the three treatment groups in either the all patient or evaluable patient population. Duration of treatment and drug compliance, for the clinically evaluable patient population, are presented in Table 43. (Volume 217 of 322, page 078, Table 11.3a.).

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Table 43. Duration of Treatment and Study Drug Compliance for Evaluable Patients According to the Applicant

Table 11.3a. Duration of Treatment and Study Drug Compliance (Evaluable Patients)

	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CLA 500 mg BID		P-value[a]
Total Treated	213		210		223		
Treatment Duration (days)							0.974
<4	1	(<1%)	3	(1%)	3	(1%)	
4 - 7	7	(3%)	6	(3%)	6	(3%)	
8 - 10	160	(75%)	154	(73%)	164	(74%)	
>10	45	(21%)	47	(22%)	50	(22%)	
Mean (SD)	10.0	(1.2)	10.0	(1.3)	10.0	(1.3)	
Minimum - Maximum[c]	[redacted]						
Compliance[b] (percentage)							0.998
<80	10	(5%)	10	(5%)	11	(5%)	
80 - 90	18	(8%)	15	(7%)	15	(7%)	
>90	185	(87%)	185	(88%)	197	(88%)	
Mean (SD)	96.4	(12.1)	96.5	(12.7)	96.4	(12.8)	
Minimum - Maximum	[redacted]						

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; SD = standard deviation

[a] P-value for F-test for testing equality of treatment means.

[b] For patients who did not return study drug containers, compliance was calculated using the number of days on treatment.

[c] Maximum extent of exposure exceeded the 10-day treatment period for some patients who did not consistently take study drug BID for 10 consecutive days.

3.2.2.4.3 Efficacy

3.2.2.4.3.1 Clinical

According to the Applicant, the primary outcome endpoint was clinical cure rate in the clinically evaluable population and outcome in the MITT population was considered supportive data.

Clinical cure rates in the evaluable population at the Post-Therapy Visit were 89% in the CDTR-PI 200 mg group, 88% in the CDTR-PI 400 mg group, and 90% in the CLA group. The 95% CI between patients treated with CDTR-PI 200 mg and CLA was (-7.3, 4.5), between patients treated with CDTR-PI 400 mg and CLA was (-7.4, 4.5), and between patients treated with CDTR-PI 200 mg and 400 mg was (-6.1, 6.3).

Clinical cure rates in the evaluable population at the Follow-Up Visit were 81% in the CDTR-PI 200 mg group, 78% in the CDTR-PI 400 mg group, and 83% in the CLA group. The 95% CI between patients treated with CDTR-PI 200 mg and CLA was (-9.9, 4.5), between patients treated with CDTR-PI 400 mg and CLA was (-12.7, 2.1), and between patients treated with CDTR-PI 200 mg and 400 mg was (-5.0, 10.4).

The Applicant's tabulations of clinical efficacy in the MITT population and the clinically evaluable population at the Post-Therapy and Follow-Up visits are summarized in Table 44. (Modified from Volume 217 page 080 and 083, Volume 218 page 130 and 162).

Table 44. Clinical Response at the Post-Therapy and Follow-Up Visits According to the Applicant

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Post-Therapy MITT Cures	191/231	(83%)	177/230	(77%)	199/243	(82%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vsCLA		0.904		[-6.1, 7.7]		
CDTR-PI 400 mg vs CLA		0.210		[-12.2,2.3]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.133		[-1.6, 13.0]		
Post-Therapy Evaluable Cures	185/209	(89%)	176/199	(88%)	196/218	(90%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CLA		0.755		[-7.3, 4.5]		
CDTR-PI 400 mg vs CLA		0.639		[-7.4, 4.5]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		>0.999		[-6.1, 6.3]		
Follow-Up MITT Cures	177/231	(77%)	170/230	(74%)	194/243	(80%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CLA		0.436		[-10.6, 4.2]		
CDTR-PI 400 mg vs CLA		0.155		[-13.5, 1.7]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.519		[-5.2, 10.6]		
Follow-Up Evaluable Cures	172/213	(81%)	164/210	(78%)	186/223	(83%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CLA		0.532		[-9.9, 4.5]		
CDTR-PI 400 mg vs CLA		0.180		[-12.7, 2.1]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.548		[-5.0, 10.4]		

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[a] P-value for comparison between treatment groups using Fisher's exact test.
[b] The 95% CI for the difference in clinical cure rates was calculated using normal approximation for the binomial distribution.

MO Comment: ***Although the Applicant stated the primary comparison for efficacy would be between the cefditoren pivoxil 400 mg arm and the comparator arm, the Applicant has made multiple comparisons between the three treatment arms without apply an appropriate statistical adjustment for***

multiple comparisons (potentially inflating the Type I Error). If only the CDTR-PI 400 mg is considered, then the Applicant's cure rate in the clinically evaluable population at Follow-Up does not demonstrate equivalence to an approved comparator (using a delta of 10%). A display of the Applicant's data incorporating an appropriate adjustment for multiple comparisons for the evaluable population at Follow-Up is displayed in Table 45. Based on the adjusted analysis the CDTR-PI 400 mg group still does not demonstrate equivalence to an approved comparator (using a delta of 10%) and the CDTR-PI 200 mg group is border line (with a CI of –10.9, 5.6). In this study the CDTR-PI 200 mg and CDTR-PI 400 mg groups do demonstrate similarity (CI, –6.2, 11.5).

Table 45. Clinical Response in Clinically Evaluable Patients at the Follow-Up Visit According to the Applicant Using 97.5% CI to Adjust for Multiple Comparisons

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Follow-Up Evaluable Cures	172/213	(81%)	164/210	(78%)	186/223	(83%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-10.9, 5.6]			
CDTR-PI 400 mg vs CLA			[-13.8, 3.2]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-6.2, 11.5]			

When the Applicant's data was reanalyzed (by the FDA Biostatistics reviewer) applying the evaluability and outcome criteria defined by the MO, clinical cure rates in the evaluable population at the Post-Therapy Visit were 79% (115/146) in the CDTR-PI 200 mg group, 70% (95/135) in the CDTR-PI 400 mg group, and 79% (122/154) in the CLA group. The 97.5% CI between patients treated with CDTR-PI 200 mg and CLA was (-11.0, 10.1), between patients treated with CDTR-PI 400 mg and CLA was (-20.3, 2.6), and between patients treated with CDTR-PI 200 mg and 400 mg was (-3.2, 20.0).

Clinical cure rates, according to the MO's criteria, in the evaluable population at the Follow-Up Visit were 51% (74/146) in the CDTR-PI 200 mg group, 43% (58/135) in the CDTR-PI 400 mg group, and 55% (84/154) in the CLA group. The 97.5% CI between patients treated with CDTR-PI 200 mg and CLA was (-16.8, 9.1), between patients treated with CDTR-PI 400 mg and CLA was (-24.7, 1.5), and between patients treated with CDTR-PI 200 mg and 400 mg was (-5.5, 21.0).

The confidence interval around the difference in efficacy rates, in the MO's evaluable population at Follow-Up, does not suggest equivalence between the comparator and the CDTR-PI 200 mg group or the CDTR-PI 400 mg group. However, the CI between the CDTR-PI 200 mg group and the CDTR-PI 400 mg group suggests statistical similarity.

The MO's tabulations of clinical efficacy in the MITT population and the clinically evaluable population at the Post-Therapy and Follow-Up visits are summarized in Table 46.

Table 46. Clinical Response at the Post-Therapy and Follow-Up Visits According to the MO

Clinical Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Post-Therapy MITT Cures	129/165	(78%)	102/156	(65%)	134/173	(78%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-9.4, 10.9]			
CDTR-PI 400 mg vs CLA			[-23.2, -1.0]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[1.6, 24.0]			
Post-Therapy Evaluable Cures	115/146	(79%)	95/135	(70%)	122/154	(79%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-11.0, 10.1]			
CDTR-PI 400 mg vs CLA			[-20.3, 2.6]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.2, 20.0]			
Follow-Up MITT Cures	78/165	(47%)	60/156	(39%)	90/173	(52%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.9, 7.4]			
CDTR-PI 400 mg vs CLA			[-25.8, 1.4]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.2, 21.2]			
Follow-Up Evaluable Cures	74/146	(51%)	58/135	(43%)	84/154	(55%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-16.8, 9.1]			
CDTR-PI 400 mg vs CLA			[-24.7, 1.5]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-5.6, 21.0]			

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin
n/N = number of evaluable patients with clinical response/total number of evaluable patients
[b] The 97.5% CI for the difference in clinical cure rates was used to adjust for multiple comparisons

<u>Statistical Reviewer's comments:</u> The Applicant's ITT(MITT) population was reclassified by excluding patients who had negative pretreatment sputum sample with at least one protocol defined respiratory pathogen and the gran stain at the central lab to be "good" and that the patient had at least two pre-treatment signs or symptoms.

After the reclassification, there is substantial reduction in the evaluability rate compared to the applicant's analyses. The clinically evaluable subjects at the test-of-cure visit is 51% in CDTR-PI 200 mg group, 43% in CDTR-PI 400 mg group and 55% in CLA 500 mg group as given in Table 46.

At the follow-up visit, the evaluable cures were substantially low as given in table 46 and the 97.5% CI for the patients treated with CDTR-PI 200 mg and CLA 500 mg was (-16.8,9.1), with CDTR-PI 400 mg and CLA 500 mg was (-24.7, 1.5) and between CDTR-PI 200 mg and 400 mg was (-5.6, 21.0). The evidence do not suggest any similarity between CDTR-PI 200 mg or CDTR-PI 400 mg to its approved comparator CLA 500 mg, adjusting for the multiplicity and using a delta of 10%.

3.2.2.4.3.2 Microbiologic

According to the Applicant, microbiologic cure rates in the evaluable population at the Post-Therapy Visit were 76% in the CDTR-PI 200 mg group, 74% in the CDTR-PI 400 mg group, and 82% in the CLA group. The 95% CI between patients treated with CDTR-PI 200 mg and CLA was (-12.9, 2.6), between patients treated with CDTR-PI 400 mg and CLA was (-15.3, 0.7), and between patients treated with CDTR-PI 200 mg and 400 mg was (-6.2, 10.6).

Microbiologic cure rates in the evaluable population at the Follow-Up Visit were 71% in the CDTR-PI 200 mg group, 67% in the CDTR-PI 400 mg group, and 71% in the CLA group. The 95% CI between patients treated with CDTR-PI 200 mg and CLA was (-9.0, 8.0), between patients treated with CDTR-PI 400 mg and CLA was (-12.7,4.7), and between patients treated with CDTR-PI 200 mg and 400 mg was (-5.2, 12.4).

The Applicant's tabulations of microbiologic efficacy in the MITT population and the microbiologically evaluable population at the Post-Therapy and Follow-Up visits are summarized in Table 47. (modified from Volume 217 of 322, page 086 and page 089 and Volume 218 of 322, page 194 and page 224).

Table 47. Microbiologic Response at the Post-Therapy and Follow-Up Visits According to the Applicant

Microbiologic Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Post-Therapy MITT Cures	165/231	(71%)	154/230	(67%)	183/243	(75%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CLA		0.351		[-11.8, 4.1]		
CDTR-PI 400 mg vs CLA		0.053		[-16.5, -0.2]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.314		[-3.9, 12.9]		
Post-Therapy Evaluable Cures	159/208	(76%)	147/198	(74%)	177/217	(82%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CLA		0.233		[-12.9, 2.6]		
CDTR-PI 400 mg vs CLA		0.076		[-15.3, 0.7]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.646		[-6.2, 10.6]		
Follow-Up MITT Cures	158/231	(68%)	145/230	(63%)	167/243	(69%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CLA		>0.999		[-8.7, 8.0]		
CDTR-PI 400 mg vs CLA		0.208		[-14.2, 2.9]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.240		[-3.3, 14.0]		
Follow-Up Evaluable Cures	152/215	(71%)	141/210	(67%)	158/222	(71%)
Comparison of Cure Rates		**P-value[a]**		**95% CI for Difference in Cure Rate[b]**		
CDTR-PI 200 mg vs CLA		0.917		[-9.0, 8.0]		
CDTR-PI 400 mg vs CLA		0.404		[-12.7, 4.7]		
CDTR-PI 200 mg vs CDTR-PI 400 mg		0.464		[-5.2, 12.4]		

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[a] P-value for comparison between treatment groups using Fisher's exact test.
[b] The 95% CI for the difference in microbiologic cure rates was calculated using normal approximation for the binomial distribution.

MO Comment: ***Although the Applicant stated the primary comparison for efficacy would be between the cefditoren pivoxil 400 mg arm and the comparator arm, the Applicant has made multiple comparisons between the three treatment arms without apply an appropriate statistical adjustment for multiple comparisons (potentially inflating the Type I Error). If only the CDTR-PI 400 mg is considered, the Applicant's cure rate, in the microbiologically evaluable population at Follow-Up does not demonstrates equivalence to an approved comparator based on a delta of 10%. Of interest, at the Post-Therapy visit in both the MITT population (p = 0.053) and the evaluable population (p =***

0.076) CDTR-PI 400 mg is close to being statistically inferior. A display of the Applicant's data incorporating an appropriate adjustment for multiple comparisons for the evaluable population at Follow-Up is displayed in Table 48. Based on the adjusted analysis the CDTR-PI 400 mg group still does not demonstrate equivalence to an approved comparator; however, CDTRI-PI 200 mg does demonstrate equivalence (using a delta of 10%).

Table 48. Microbiologic Response in Microbiologically Evaluable Patients at the Follow-Up Visit According to the Applicant Using 97.5% CI to Adjust for Multiple Comparisons

Microbiologic Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Follow-Up						
Evaluable Cures	152/215	(71%)	141/210	(67%)	158/222	(71%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-10.2, 9.3]			
CDTR-PI 400 mg vs CLA			[-14.0, 15.9]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-6.5, 13.6]			

When the Applicant's data was reanalyzed (by the FDA Biostatistics reviewer) applying the evaluability and outcome criteria defined by the MO, microbiologic cure rates in the evaluable population at the Post-Therapy Visit were 75% (106/142) in the CDTR-PI 200 mg group, 72% (90/125) in the CDTR-PI 400 mg group, and 79% (121/153) in the CLA group. The 97.5% CI between patients treated with CDTR-PI 200 mg and CLA was (-15.5, 6.6), between patients treated with CDTR-PI 400 mg and CLA was (-18.7, 4.5), and between patients treated with CDTR-PI 200 mg and 400 mg was (-9.5, 14.8).

Microbiologic cure rates, according to the MO, in the evaluable population at the Follow-Up Visit were 57% (83/145) in the CDTR-PI 200 mg group, 47% (64/135) in the CDTR-PI 400 mg group, and 54% (82/152) in the CLA group. The 97.5% CI between patients treated with CDTR-PI 200 mg and CLA was (-9.6, 16.2), between patients treated with CDTR-PI 400 mg and CLA was (-19.8, 6.7), and between patients treated with CDTR-PI 200 mg and 400 mg was (-3.4, 23.2).

The confidence intervals around the difference in efficacy rates, in the MO's evaluable population at Follow-Up, between the CDTR-PI 200 mg group and the CLA group suggests equivalence; however, the confidence intervals around the difference in efficacy rates for the CDTR-PI 400 mg group and the CLA group does not demonstrate equivalence (if a delta of 10% is required).

The MO's tabulations of microbiologic efficacy in the MITT population and the microbiologically evaluable population at the Post-Therapy and Follow-Up visits are summarized in Table 49.

Table 49. Microbiologic Response at the Post-Therapy and Follow-Up Visits According to the MO

Microbiologic Response	CDTRI-PI 200 mg BID n/N (%)		CDTRI-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Post-Therapy MITT Cures	110/165	(67%)	90/156	(58%)	123/173	(71%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-15.7, 6.9]			
CDTR-PI 400 mg vs CLA			[-25.2, -1.7]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.1, 21.1]			
Post-Therapy Evaluable Cures	106/142	(75%)	90/125	(72%)	121/153	(79%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-15.5, 6.6]			
CDTR-PI 400 mg vs CLA			[-18.7, 4.6]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-9.5, 14.8]			
Follow-Up MITT Cures	86/165	(52%)	65/156	(42%)	87/173	(50%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-10.4, 14.0]			
CDTR-PI 400 mg vs CLA			[-20.9, 3.7]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-2.0, 22.9]			
Follow-Up Evaluable Cures	83/145	(57%)	64/135	(47%)	82/152	(54%)
Comparison of Cure Rates			**97.5% CI for Difference in Cure Rate[b]**			
CDTR-PI 200 mg vs CLA			[-9.6, 16.2]			
CDTR-PI 400 mg vs CLA			[-19.8, 6.7]			
CDTR-PI 200 mg vs CDTR-PI 400 mg			[-3.5, 23.2]			

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin
n/N = number of evaluable patients with microbiologic response/total number of evaluable patients
[b] The 97.5% CI for the difference in microbiologic cure rates was used to adjust for multiple comparisons

<u>Statistical Reviwer's comments:</u> The applicant's analysis results of the Microbiologic responses at the post-therapy and follow-up are given in table 47. Multiplicity adjustments were applied as before, for the three treatments arm comparisons and the 97.5% CI for the microbiologic responses at the follow-up visit are given in Table 48. Using a delta of 10%, CDTR-PI 400 mg does not demonstrate a similarity to the comparator CLA 500 mg. Also, based on the Applicant's results in Table 47, at the post-therapy visit in the MITT

population, CDTR 400mg is at the boarder line significance (p=0.053, 95% CI: -16.5,-0.2) for not being statistically inferior to the comparator. The CDTR-PI 200 mg demonstrates similarity to the approved drug CLA 500 mg BID, using a delta of 10%.

The data was re-analyzed for the post therapy and follow up visits after applying the evaluability and outcome criteria and the analyses results are given in table 49. It is apparent from the table that the cure rates were considerably reduced at the follow-up.

The 97.5% confidence intervals for the difference in microbiologic cure rates in the evaluable and MITT population at follow-up, the CDTR-PI 400 mg compared to the approved comparator CLA 500 mg BID, failed to demonstrate any equivalence and CDTR-PI 200 mg suggests similarity to CLA500 mg BID, considering a delta of 10%.

3.2.2.4.3.3 Pathogen Eradication

According to the Applicant, no statistically significant pairwise differences were observed in overall pathogen eradication rates at the Post-Therapy or Follow-Up visits. Of all causative respiratory pathogens isolated at pretreatment, 79% were eradicated in the CDTR-PI 200 mg group, 78% were eradicated in the CDTR-PI 400 mg group, and 83% were eradicated in the CLA group at the Post-Therapy visit. Of all causative respiratory pathogens isolated at pretreatment, 73% were eradicated in the CDTR-PI 200 mg group, 70% were eradicated in the CDTR-PI 400 mg group, and 74% were eradicated in the CLA group at the Follow-Up visit. For *H. influenzae*, the eradication rate was higher in the CDTR-PI 200 mg group (88%) than in the CDTR-PI 400 mg (65%) or CLA (63%) groups. For *M. catarrhalis* and *S. aureus*, the eradication rates were higher in the CLA group (91% and 91%, respectively) than in the CDTR-PI 400 mg group (78% and 73%, respectively). Pathogen eradication rates for the microbiologically evaluable population are displayed in Table 50. (modified from Volume 217 of 322, page 092-Table 11.4e and page 095-Table 11.4g).

Table 50. Eradication Rates for Target Pathogens at the Post-Therapy and Follow-Up Visits in the Microbiologically Evaluable Population According to the Applicant.

Post-Therapy						
Pre-Therapy Pathogen	**CDTR-PI 200 mg BID n/N (%)**		**CDTR-PI 400 mg BID n/N (%)**		**CLA 500 mg BID n/N (%)**	
OVERALL	209/264	(79%)	201/259	(78%)	237/284	(83%)
H. influenzae	45/48	(94%)	36/45	(80%)	38/49	(78%)
H. parainfluenzae	100/141	(71%)	93/129	(72%)	121/152	(80%)
M. catarrhalis	22/26	(85%)	32/36	(89%)	30/31	(97%)
S. aureus	20/23	(87%)	19/24	(79%)	22/23	(96%)
S. pneumoniae	17/20	(85%)	12/15	(80%)	21/23	(91%)
S. pyogenes	1/1	(100%)	2/2	(100%)	0/0	
Other Pathogens[a]	4/5	(80%)	7/8	(88%)	5/6	(83%)

Comparison of Overall Eradication Rates	**P-value[b]**
CDTR-PI 200 mg vs CLA	0.227
CDTR-PI 400 mg vs CLA	0.103
CDTR-PI 200 mg vs CDTR-PI 400 mg	0.672

Follow-Up						
Pre-Therapy Pathogen	**CDTR-PI 200 mg BID n/N (%)**		**CDTR-PI 400 mg BID n/N (%)**		**CLA 500 mg BID n/N (%)**	
OVERALL	197/271	(73%)	194/276	(70%)	215/292	(74%)
H. influenzae	44/50	(88%)	33/51	(65%)	31/49	(63%)
H. parainfluenzae	93/144	(65%)	91/132	(69%)	110/157	(70%)
M. catarrhalis	21/26	(81%)	29/37	(78%)	31/34	(91%)
S. aureus	18/22	(82%)	19/26	(73%)	21/23	(91%)
S. pneumoniae	15/21	(71%)	15/19	(79%)	17/22	(77%)
S. pyogenes	1/1	(100%)	1/2	(50%)	1/1	(100%)
Other Pathogens[a]	5/7	(71%)	6/9	(67%)	4/6	(67%)

Comparison of Overall Eradication Rates	**P-value[b]**
CDTR-PI 200 mg vs CLA	0.849
CDTR-PI 400 mg vs CLA	0.401
CDTR-PI 200 mg vs CDTR-PI 400 mg	0.570

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment
[a] Include *Haemophilus parahaemolyticus, Haemophilus haemolyticus, Klebsiella pneumoniae, Neisseria meningitidis, Proteus mirabilis,* and *Streptococcus agalactiae.*
[b] P-value for comparison between treatment groups using Fisher's exact test.

The Applicant also assessed eradication rates for selected pathogens classified by pretreatment penicillinase production, oxacillin resistance and/or penicillin resistance at the Post-Therapy and Follow-Up visits. At Follow-Up, for penicillinase-producing *H. influenzae*, the eradication rate was higher in the CDTR-PI 200 mg group (88%) than in the CLA group (64%); for penicillinase-producing *M. catarrhalis*, the eradication rate was higher in the CLA group (93%) than in the CDTR-PI 200 mg (79%) or CDTR-PI 400 mg (76%) groups; for penicillinase-producing and

penicillin-resistant *S. aureus*, eradication rates were higher in the CLA group (91% and 91%, respectively) than in the CDTR-PI 400 mg group (71% and 68%, respectively). Pathogen eradication rates for selected resistant pathogens in the microbiologically evaluable population are displayed in Table 51. (modified from Volume 217 of 322, page 093-Table 11.4f and page 096-Table 11.4h).

Statistical Reviwer's comments:

The sponsor has reported p-value in Table 50 and that is incorrect in equivalence trials. Also, each patient may have multiple pathogens and the observations cannot be treated as independent.

Table 51. Eradication Rates for Selected Penicillinase-Producing, Oxacillin-Resistant, and/or Penicillin-Resistant Pathogens at the Post-Therapy and Follow-Up Visits in Microbiologically Evaluable Patients According to the Applicant

Post-Therapy						
Pre-Therapy Pathogen	**CDTR-PI 200 mg BID n/N (%)**		**CDTR-PI 400 mg BID n/N (%)**		**CLA 500 mg BID n/N (%)**	
Penicillinase-Producing Pathogens						
H. influenzae	14/16	(88%)	7/10	(70%)	7/10	(70%)
H. parainfluenzae	5/8	(63%)	9/13	(69%)	8/10	(80%)
M. catarrhalis	20/24	(83%)	28/32	(88%)	26/27	(96%)
S. aureus	18/21	(86%)	17/22	(77%)	21/22	(95%)
Oxacillin-Resistant Pathogens						
S. aureus	1/2	(50%)	1/1	(100%)	1/1	(100%)
Penicillin-Resistant Pathogens						
S. aureus	16/17	(94%)	15/20	(75%)	21/22	(95%)
S. pneumoniae	3/4	(75%)	2/2	(100%)	2/3	(67%)
Follow-UP						
Pre-Therapy Pathogen	**CDTR-PI 200 mg BID n/N (%)**		**CDTR-PI 400 mg BID n/N (%)**		**CLA 500 mg BID n/N (%)**	
Penicillinase-Producing Pathogens						
H. influenzae	15/17	(88%)	8/11	(73%)	7/11	(64%)
H. parainfluenzae	5/8	(63%)	9/13	(69%)	5/10	(50%)
M. catarrhalis	19/24	(79%)	25/33	(76%)	28/30	(93%)
S. aureus	17/21	(81%)	17/24	(71%)	20/22	(91%)
Oxacillin-Resistant Pathogens						
S. aureus	0/1	(0%)	1/1	(100%)	1/1	(100%)
Penicillin-Resistant Pathogens						
S. aureus	14/16	(88%)	15/22	(68%)	20/22	(91%)
S. pneumoniae	2/4	(50%)	2/2	(100%)	2/3	(67%)

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment

MO Comment: ***When the Applicant's data was reanalyzed (by the FDA Biostatistics reviewer) applying the evaluability and outcome criteria defined by the MO, overall pathogen eradication rates in the microbiologically evaluable population were 76% (209/275) in the CDTR-PI 200 mg group, 73% (184/253) in the CDTR-PI 400 mg group, and 80% (248/310) in the CLA group at the***

Post-Therapy Visit and 75% (206/276) in the CDTR-PI 200 mg group, 68% (179/262) in the CDTR-PI 400 mg group, and 74% (227/308) in the CLA group at the Follow-Up visit. At Post-Therapy and Follow-Up the eradication rate for H. influenzae (83% and 85% respectively) appears to be better for the CDTR-PI 200 mg group than for the CLA group (72% and 66% respectively) or the CDTR-PI 400 mg group (67% and 61% respectively). At Post-Therapy and Follow-Up the eradication rate for S. aureus (82% and 88% respectively) appears to be better for the CLA 500 mg group than for the CDTR-PI 200 mg group (76% and 76% respectively) or the CDTR-PI 400 mg group (71% an71% respectively). Pathogen eradication rates, according to the MO, for the microbiologically evaluable population are displayed in Table 52. Eradication rates for selected resistant pathogens, according to the MO, in the microbiologically evaluable population are displayed in Table 53.

Table 52. Eradication Rates for Target Pathogens at the Post-Therapy and Follow-Up Visits in the Microbiologically Evaluable Population According to the MO.

Post-Therapy Visit

Pre-Therapy Pathogen	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
OVERALL	209/275	(76%)	184/253	(73%)	248/310	(80%)
**H. influenzae*	49/59	(83%)	30/45	(67%)	43/60	(72%)
**H. parainfluenzae*	102/144	(71%)	93/133	(70%)	139/174	(80%)
**M. catarrhalis*	25/30	(83%)	35/41	(85%)	32/35	(91%)
**S. aureus*	19/25	(76%)	15/21	(71%)	16/19	(84%)
**S. pneumoniae*	13/16	(81%)	11/13	(85%)	18/22	(82%)
S. pyogenes	1/1	(100%)	0/0	-	0/0	-
Other Pathogens[a]	-		-		-	

Follow-Up Visit

Pre-Therapy Pathogen	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
OVERALL	206/276	(75%)	179/262	(68%)	227/308	(74%)
**H. influenzae*	50/59	(85%)	30/49	(61%)	38/58	(66%)
**H. parainfluenzae*	101/146	(69%)	91/134	(68%)	129/174	(74%)
**M. catarrhalis*	26/32	(81%)	31/43	(72%)	30/37	(81%)
**S. aureus*	16/21	(76%)	15/21	(71%)	15/17	(88%)
**S. pneumoniae*	12/17	(71%)	12/15	(80%)	14/21	(67%)
S. pyogenes	1/1	(100%)	0/0	-	1/1	(100%)
Other Pathogens[a]	-	-	-	-	-	-

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment
[a] Not included in MO analysis
[b] P-value for comparison between treatment groups using Fisher's exact test.
* Pathogens sought in the label.

Table 53. Eradication Rates for Selected Penicillinase-Producing, Oxacillin-Resistant, and/or Penicillin-Resistant Pathogens at the Post-Therapy and Follow-Up Visits in Microbiologically Evaluable Patients According to the MO

Post-Therapy Visit						
Pre-Therapy Pathogen	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Penicillinase-Producing Pathogens						
H. influenzae	12/19	(63%)	2/8	(25%)	10/14	(71%)
H. parainfluenzae	8/12	(67%)	7/14	(50%)	8/9	(89%)
M. catarrhalis	22/27	(82%)	29/35	(83%)	27/30	(90%)
S. aureus	15/21	(71%)	15/21	(71%)	16/19	(84%)
Oxacillin-Resistant Pathogens						
S. aureus	2/4	(50%)	3/3	(100%)	0/1	(0%)
Penicillin-Resistant Pathogens						
S. aureus	13/15	(87%)	13/19	(68%)	16/19	(84%)
S. pneumoniae	2/3	(67%)	3/4	(75%)	3/5	(60%)
Follow-Up Visit						
Pre-Therapy Pathogen	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
Penicillinase-Producing Pathogens						
H. influenzae	15/19	(79%)	4/7	(57%)	10/15	(67%)
H. parainfluenzae	9/12	(75%)	7/13	(54%)	5/9	(56%)
M. catarrhalis	23/29	(79%)	25/37	(68%)	27/32	(84%)
S. aureus	14/19	(74%)	15/21	(71%)	15/17	(88%)
Oxacillin-Resistant Pathogens						
S. aureus	-	-	2/3	(67%)	-	-
Penicillin-Resistant Pathogens						
S. aureus	10/11	(91%)	13/19	(68%)	15/17	(88%)
S. pneumoniae	2/3	(67%)	3/3	(100%)	2/5	(40%)

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin
n/N = number of pathogens eradicated/number of pathogens isolated pretreatment

3.2.2.4.3.4 Secondary Efficacy Variable

According to the Applicant, there were no statistically significant pairwise differences in the percentage of evaluable patients showing resolution and improvement in sputum appearance, sputum volume, and dyspnea, or resolution in fever, rales, rhonchi, wheezes, or cyanosis at the Follow-Up Visit. A statistically significant treatment difference was observed between the CDTR-PI 200 mg and CDTR-PI 400 groups in cough, with 12% of the CDTR-PI 200 mg patients and 20% of the CDTR-PI 400 mg patients showing resolution of this symptom (p=0.046).

MO Comment: ***The time to resolution of these signs and symptoms, for the indication of AECB, has not been shown to affect overall outcome.***

3.2.2.4.4 Safety

3.2.2.4.4.1 Adverse Events

Total enrollment for this study was 903 patients. Of these 297 were in the CDTR-PI 200 mg arm, 302 were in the CDTR-PI 400 mg arm, and

304 were in the CLA arm. No patients were excluded from the safety database. The number of adverse events, drug-related events, serious adverse events, and withdrawals from the study due to adverse events during treatment (between study day 1 and 3 days post-therapy) and during post-treatment (at least 4 days post-therapy) by treatment arm is summarized in Table 54. (Volume 217 of 322, pages 110-124).

Table 54. Summary of Adverse Events in the "All" Population According to the Applicant

	CDTR-PI 200 mg BID n/N (%)		CDTR-PI 400 mg BID n/N (%)		CLA 500 mg BID n/N (%)	
During Treatment (Study Day 1 to 3 Days Post-Therapy)						
Any AE	112/297	(38%)	125/302	(41%)	143/304	(47%)
Any Drug Related AE	76/297	(26%)	92/302	(30%)	109/304	(36%)
Any Serious AE	10/297	(3%)	9/302	(3%)	6/304	(2%)
Prematurely Discont. Due to AE	11/297	(4%)	11/302	(4%)	13/304	(4%)
Post-Therapy (At Least 4 Days the Last Dose of Study Drug)						
Any AE	34/297	(11%)	36/302	(12%)	34/304	(11%)
Any Drug Related AE	4/297	(1%)	4/302	(1%)	5/304	(2%)

CDTR-PI = cefditoren pivoxil; CXM-AX = cefuroxime axetil
n/N=number of patients with event/total number of patients

3.2.2.4.4.1.1 All AEs

According to the Applicant, during treatment, 112 (38%) patients in the CDTR-PI 200 mg group, 125 (41%) patients in the CDTR-PI 400 mg group, and 143 (47%) patients in the CLA group reported at least one adverse event. The difference between the CDTR-PI 200 mg and CLA groups was statistically significant (p=0.021). The most commonly reported adverse events during treatment were diarrhea (11%) and headache (7%) in the CDTR-PI 200 mg group; diarrhea (17%) and vaginal moniliasis (9% of female patients) in the CDTR-PI 400 mg group; and taste perversion (12%), diarrhea (10%), and nausea (8%) in the CLA group. Statistically significant differences were observed in the incidence of diarrhea, dry mouth, taste perversion, and vaginal moniliasis among females. Diarrhea was reported by 11% of the CDTR-PI 200 mg patients, 17% of the CDTR-PI 400 mg patients, and 10% of the CLA patients; the differences between the two cefditoren groups (p=0.043) and between the CDTR-PI 400 mg and CLA groups (p=0.011) were statistically significant. Dry mouth was reported by 7 (2%) CLA patients and none of the CDTR-PI 200 mg patients (p=0.015). Taste perversion was reported by 4 (1%) patients in each CDTR-PI group and by 36 (12%) patients in the CLA group (p<0.001 for each comparison). Vaginal moniliasis was reported by 4 (3%) female patients in the CDTR-PI 200 mg group and 14 (9%) female patients in the CDTR-PI 400 mg group (p=0.028).

Thirteen severe events were reported in the CDTR-PI 200 mg group (dyspnea and pneumonia by 2 patients each, and abdominal pain, anaphylactoid reaction, pain, congestive heart failure, tachycardia, cholelithiasis, diarrhea, pleural disorder, and vaginal moniliasis by 1 patient each). Fifteen severe events were reported in the CDTR-PI 400 mg group (diarrhea by 2 patients, abdominal pain, accidental injury, asthenia, back pain, congestive heart failure, creatinine increased, diabetes mellitus, myalgia, dizziness, insomnia, dyspnea, pneumonia, and respiratory disorder by 1 patient each). Fourteen severe events were reported in the CLA group (nausea and taste perversion by 2 patients each, and accidental overdose, headache, pain, diarrhea, myalgia, anxiety, asthma, cough increased, respiratory disorder, and otitis media by 1 patient each).
A summary of all adverse events during treatment reported by ≥2% of patients in any of the three treatment groups is presented by treatment group in Table 55. (Volume 317 of 322, page 112).

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Table 55. Summary of Common Adverse Events Grouped by COSTART Term, During Treatment, According to the Applicant

	CDTR-PI 200 mg BID (N=297)					CDTR-PI 400 mg BID (N=302)					CLA 500 mg BID (N=304)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[@c]				112	38%				125	41%				143	47%
BODY AS A WHOLE				42	14%				40	13%				39	13%
Headache	11	10	0	21	7%	9	8	0	17	6%	8	9	1	18	6%
Abdominal pain	2	3	1	6	2%	7	4	1	12	4%	5	1	0	6	2%
DIGESTIVE SYSTEM[&]				59	20%				82	27%				68	22%
Diarrhea[&#]	20	11	1	32	11%	31	17	2	50	17%	24	4	1	29	10%
Nausea	10	4	0	14	5%	15	3	0	18	6%	16	6	2	24	8%
Dyspepsia	3	1	0	4	1%	9	2	0	11	4%	5	1	0	6	2%
Vomiting	1	4	0	5	2%	3	2	0	5	2%	1	7	0	8	3%
Constipation	4	1	0	5	2%	1	2	0	3	1%	2	1	0	3	1%
NERVOUS SYSTEM[@]				11	4%				15	5%				28	9%
Dizziness	4	1	0	5	2%	2	0	1	3	1%	3	0	0	3	1%
Insomnia	0	1	0	1	<1%	1	2	1	4	1%	4	1	0	5	2%
Dry Mouth[@]	0	0	0	0	0%	1	0	0	1	<1%	4	3	0	7	2%
SKIN AND APPENDAGES[#]				7	2%				3	1%				12	4%
Rash	0	0	0	0	0%	0	0	0	0	0%	3	2	0	5	2%
SPECIAL SENSES[@#]				7	2%				13	4%				38	13%
Taste Perversion[@#]	4	0	0	4	1%	2	2	0	4	1%	24	10	2	36	12%
UROGENITAL SYSTEM (FEMALES)[&d]				(N=151) 4	3%				(N=163) 14	9%				(N=162) 6	4%
Vaginal Moniliasis[&d]	2	1	1	4	3%	9	5	0	14	9%	4	2	0	6	4%

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; Mod = moderate; Sev = severe

[&] Statistically significant difference between CDTR-PI 200 mg and CDTR-PI 400 mg, p≤0.05.

[@] Statistically significant difference between CDTR-PI 200 mg and CLA, p≤0.05.

[#] Statistically significant difference between CDTR-PI 400 mg and CLA, p≤0.05.

[a] Adverse events occurring in ≥2% of patients in any treatment group.

[b] Table summarizes the most severe occurrence of each COSTART term from each patient.

[c] Number of patients with one or more adverse events.

[d] Gender-specific adverse event; percentage given is of females only.

According to the Applicant, during posttreatment, 34 (11%) patients in the CDTR-PI 200 mg group, 36 (12%) patients in the CDTR-PI 400 mg group, and 34 (11%) patients in the CLA group reported at least one adverse event. Anxiety was reported by 5 (2%) patients in the CDTR-PI 400 mg group and no patient in the other two treatment groups; the difference between the CDTR-PI 400 mg and CLA groups was statistically significant (p=0.030). Pharyngitis was reported by 5 (2%) patients in the CDTR-PI 200 mg group and no patient in the CDTR-PI 400 mg group, a statistically significant difference (p=0.029). No other specific adverse event reported by patients in the three treatment groups had an incidence greater than

1% during posttreatment. Six severe events (headache, peritonitis, tachycardia, myalgia, lung disorder, and pneumonia) were reported in the CDTR-PI 200 mg group, six severe events (dyspnea by 2 patients, and headache, migraine, diarrhea, and pleural effusion by 1 patient each) were reported in the CDTR-PI 400 mg group, and five severe events (infection, pain, heart arrest, myocardial infarct, and angioedema) were reported in the CLA group during posttreatment.

3.2.2.4.4.1.2 Treatment Related AEs

According to the Applicant, during treatment, 76 (26%) patients in the CDTR-PI 200 mg group, 92 (30%) patients in the CDTR-PI 400 mg group, and 109 (36%) patients in the CLA group reported at least one adverse that was considered by the investigator to be possibly, probably, or definitely treatment-related. The difference between the CDTR-PI 200 mg and CLA groups was statistically significant (p=0.008). The most frequently occurring treatment-related adverse events were diarrhea (11%) in the CDTR-PI 200 mg group; diarrhea (15%) and vaginal moniliasis (9% of female patients) in the CDTR-PI 400 mg group; and taste perversion (12%), diarrhea (10%), and nausea (8%) in the CLA group. Statistically significant pairwise differences were observed in the incidence of diarrhea, constipation, vomiting, dry mouth, taste perversion, and vaginal moniliasis among females. Diarrhea was reported by 45 (15%) patients in the CDTR-PI 400 mg group and 29 (10%) patients in the CLA group (p=0.048). Constipation was reported by 5 (2%) patients in the CDTR-PI 200 mg group and no patients in the CDTR-PI 400 mg group (p=0.029). Vomiting was reported by 8 (3%) patients in the CLA group and 1 (<1%) patient in the CDTR-PI 200 mg group (p=0.038). Dry mouth was reported by 6 (2%) patients in the CLA group and no patients in the CDTR-PI 200 mg group (p=0.031). Taste perversion was reported by 36 (12%) patients in the CLA group and by 4 (1%) patients in each of the CDTR-PI groups (p<0.001 for both comparisons). Vaginal moniliasis was reported by 4 (3%) females in the CDTR-PI 200 mg group and 14 (9%) females in the CDTR-PI 400 mg group (p=0.028).

Three severe treatment-related adverse events were reported in the CDTR-PI 200 mg group (abdominal pain, diarrhea and vaginal moniliasis by 1 patient each). Five severe treatment-related adverse events were reported in the CDTR-PI 400 mg group (diarrhea by 2 patients; asthenia, creatinine increased, and myalgia by 1 patient each). Nine severe treatment-related adverse events were reported in the CLA group (nausea and taste perversion by 2 patients each, and accidental overdose, headache, pain, diarrhea, and anxiety by 1 patient each). A summary of treatment-related adverse events,

reported by ≥2% of patients in any treatment group, is presented by treatment group in Table 56. (Volume 317 of 322, page 113).

Table 56. Summary of Common Treatment-Related Adverse Events Grouped by COSTART Term, During Treatment, According to the Applicant

	CDTR-PI 200 mg BID (N=297)					CDTR-PI 400 mg BID (N=302)					CLA 500 mg BID (N=304)				
	Severity[b]					Severity[b]					Severity[b]				
Adverse Events	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%	Mild	Mod	Sev	Total	%
OVERALL[@c]				76	26%				92	30%				109	36%
BODY AS A WHOLE				21	7%				14	5%				17	6%
Headache	5	7	0	12	4%	3	3	0	6	2%	4	3	1	8	3%
Abdominal Pain	2	2	1	5	2%	3	3	0	6	2%	5	1	0	6	2%
DIGESTIVE SYSTEM				50	17%				69	23%				65	21%
Diarrhea[#]	20	11	1	32	11%	26	17	2	45	15%	24	4	1	29	10%
Nausea	10	3	0	13	4%	13	3	0	16	5%	15	6	2	23	8%
Dyspepsia	1	1	0	2	1%	8	1	0	9	3%	4	1	0	5	2%
Constipation[&]	4	1	0	5	2%	0	0	0	0	0%	2	1	0	3	1%
Vomiting[@]	0	1	0	1	<1%	1	2	0	3	1%	1	7	0	8	3%
NERVOUS SYSTEM[@#]				7	2%				6	2%				20	7%
Insomnia	0	1	0	1	<1%	0	1	0	1	<1%	4	1	0	5	2%
Dry Mouth[@]	0	0	0	0	0%	1	0	0	1	<1%	3	3	0	6	2%
SPECIAL SENSES[@#]				4	1%				7	2%				36	12%
Taste Perversion[@#]	4	0	0	4	1%	2	2	0	4	1%	24	10	2	36	12%
UROGENITAL SYSTEM (FEMALES)[&d]				(N=151) 4	3%				(N=163) 14	9%				(N=162) 6	4%
Vaginal Moniliasis[&d]	2	1	1	4	3%	9	5	0	14	9%	4	2	0	6	4%

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; Mod = moderate; Sev = severe

[&] Statistically significant difference between CDTR-PI 200 mg and CDTR-PI 400 mg, p≤0.05.

[@] Statistically significant difference between CDTR-PI 200 mg and CLA, p≤0.05.

[#] Statistically significant difference between CDTR-PI 400 mg and CLA, p≤0.05.

[a] Adverse events occurring in ≥2% of patients in any treatment group.

[b] Table summarizes the most severe occurrence of each COSTART term from each patient.

[c] Number of patients with one or more adverse events.

[d] Gender-specific adverse event; percentage given is of females only.

According to the Applicant, during posttreatment, 4 (1%) patients in the CDTR-PI 200 mg group, 4 (1%) patients in the CDTR-PI 400 mg group and 5 (2%) patients in the CLA treatment group reported at least one treatment-related adverse event. In the CDTR-PI 200 mg group, constipation was reported by 2 patients, lung disorder and atelectasis were reported by 1 patient each, and nausea and vomiting was reported by 1 patient; in the CDTR-PI 400 mg group, headache, diarrhea, hemorrhagic colitis, weight loss and myalgia were reported by 1 patient each; in the CLA group, diarrhea, oral moniliasis, sinusitis, rash, and vaginal moniliasis were reported by 1 patient each. Two severe adverse events (headache, diarrhea) were reported by

patients in the CDTR-PI 400 mg group during posttreatment; all other treatment-related adverse events were mild or moderate in intensity.

3.2.2.4.4.1.3 Discontinuations Due to AE

According to the Applicant, 35 patients were prematurely discontinued from study drug due to the occurrence of at least one adverse event: 11 in the CDTR-PI 200 mg group, 11 in the CDTR-PI 400 mg group, and 13 in the CLA group. The majority of the adverse events leading to discontinuation in all three treatment groups were associated with the digestive system. A summary of patients who prematurely discontinued treatment due to adverse events is presented by treatment group in Table 57. (Volume 317 of 322, page 125).

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Table 57. Patients Who Prematurely Discontinued Treatment Due to Adverse Events According to the Applicant

Investigator Patient Number	Age/Sex	Day of Onset[a]	Day of Resolution[a]	Body System	COSTART Term
Patients Discontinued from the Cefditoren Pivoxil 200 mg BID Treatment Group					
Christensen 6375	24/F	1	12 (3)	Body as a whole	Asthenia[b]
		3	8	Skin & appendages	Alopecia[b]
		7	12 (3)	Respiratory	Rhinitis[b]
		8	12 (3)	Urogenital	Vaginal moniliasis[b]
Cobb 6512	54/F	5 (0)	11 (6)	Body as a whole	Abdominal pain[b]
Durden 5313	75/F	7 (0)	14 (7)	Digestive	Cholelithiasis
		7 (0)	14 (7)	Respiratory	Dyspnea
Fogarty 6310	77/M	1	4 (1)	Digestive	Nausea[b]
		1	4 (1)	Digestive	Vomiting[b]
Hall 6263	30/F	7	8 (0)	Urogenital	Vaginal moniliasis[b]
Hyers 5713	36/F	2	90 (82)	Digestive	Diarrhea[b]
Poling 5055	69/F	1	3 (1)	Metabolic & nutritional	Edema[b]
		2 (0)	3 (1)	Skin & appendages	Urticaria[b]
Poling 5430	22/M	5 (1)	51 (47)	Respiratory	Pneumonia
Rodrigues 5643	45/F	5	[15 hrs]	Digestive	Diarrhea[b]
Sachs 5504	81/M	4 (0)	14 (10)	Respiratory	Pneumonia
		4 (0)	14 (10)	Respiratory	Dyspnea
Stewart 5657	56/F	2	4 (0)	Digestive	Diarrhea[b]
		2	4 (0)	Body as a whole	Headache[b]
		2	3	Digestive	Nausea[b]
Patients Discontinued from the Cefditoren Pivoxil 400 mg BID Treatment Group					
Christensen 6384	29/F	1	5 (0)	Digestive	Diarrhea[b]
Durden 5623	51/F	2	4 (1)	Digestive	Diarrhea[b]
Fiel 5876	27/F	8 (1)	10 (3)	Digestive	Nausea[b]
Fiel 6284	45/F	2	3 (0)	Body as a whole	Asthenia[b]
		2	3 (0)	Musculoskeletal	Myalgia[b]
Ovetsky 5877	56/M	3 (0)	10 (7)	Cardiovascular	Congestive heart failure
		3 (0)	10 (7)	Respiratory	Respiratory disorder
		4 (1)	10 (7)	Respiratory	Pneumonia
Rhudy 5536	23/F	1 (0)	2 (1)	Nervous	Insomnia
		1 (0)	2 (1)	Musculoskeletal	Myalgia
Rosemore 6465	48/M	7	13 (4)	Body as a whole	Abdominal pain[b]
		7	13 (4)	Digestive	Diarrhea[b]
Simon 5386	60/F	3 (1)	10 (8)	Respiratory	Lung disorder
Simon 5390	57/M	1 (0)	3 (2)	Body as a whole	Abdominal pain[b]
		1 (0)	3 (2)	Digestive	Nausea[b]
		1 (0)	3 (2)	Digestive	Vomiting[b]
Upchurch 5659	20/F	3	7 (0)	Body as a whole	Fever
		3	7 (0)	Nervous	Dizziness
		3	7 (0)	Respiratory	Sinusitis
		7 (0)	21 (14)	Digestive	Liver function tests abnormal
Yarbrough 6357	64/F	1 (0)	[6 hrs]	Digestive	Nausea[b]
		1 (0)	[4 hrs]	Digestive	Vomiting[b]

Note: Study drug was prematurely discontinued for 1 additional patient in the CDTR-PI 400 mg group, Reina 5152, (listed in Appendix 16.2.7.4), who was classified as discontinuing primarily due to therapeutic failure with adverse event as a secondary reason.

[a] Days posttreatment are presented in parentheses; if less than 1 day, duration in hours is presented in brackets; Cont. = event continued as of specified day.

[b] Drug-relationship classified as possible, probable, or definite.

3.2.2.4.4.1.4 Serious AEs

According to the Applicant, 25 patients had a serious adverse event during the study: 10 in the CDTR-PI 200 mg group (including 1

patient who died), 9 in the CDTR-PI 400 mg group, and 6 in the CLA group (including 1 patient who died). Of the 25 patients who reported serious adverse events, only 1 patient, with diarrhea and hemorrhagic colitis on CDTR-PI 400 mg, was considered by the investigator to have a serious drug related event. A summary of patients who experienced serious adverse events is presented by treatment group in Table 58. (Volume 317 of 322, page 123).

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Table 58. Patients Who Experienced Serious Adverse Events According to the Applicant

Investigator Patient Number	Age/Sex	Day of Onset[a]	Day of Resolution[a]	Body System	COSTART Term	SAE Criteria
Patients with Serious Adverse Events in the Cefditoren Pivoxil 200 mg BID Treatment Group						
Durden 5313#	75/F	7 (0)	14 (7)	Digestive	Cholelithiasis	Hospitalization
		7 (0)	14 (7)	Respiratory	Dyspnea	Hospitalization
Goldstein 5698	56/F	22 (12)	23 (13)	Body as a whole	Myalgia	Hospitalization
Huerta 5717	75/M	14 (4)	28 (18)	Respiratory	Pneumonia	Hospitalization
Merrin 6201	58/M	12 (2)	19 (9)	Cardiovascular	Congestive heart failure	Hospitalization
		12 (2)	19 (9)	Cardiovascular	Tachycardia	Hospitalization
Mishkin 5029	74/F	16 (6)	32 (22)	Respiratory	Asthma	Hospitalization
		35 (25)	41 (31)	Body as a whole	Peritonitis	Hospitalization
Netzel 5074	85/M	31 (21)	37 (27)	Respiratory	Lung disorder	Death
Poling 5430#	22/M	5 (1)	51 (47)	Respiratory	Pneumonia	Required Intervention
Sachs 5504#	81/M	4 (0)	14 (10)	Respiratory	Pneumonia	Hospitalization
		4 (0)	14 (10)	Respiratory	Dyspnea	Hospitalization
Simon 5482	72/M	30 (20)	42 (32)	Respiratory	Lung disorder	Hospitalization
		30 (20)	39 (29)	Body as a whole	Infection	Hospitalization
Williams, II 5261	53/F	13 (3)	14 (4)	Body as a whole	Anaphylactoid reaction	Life-threatening
Patients with Serious Adverse Events in the Cefditoren Pivoxil 400 mg BID Treatment Group						
Block 5185	70/M	22 (12)	25 (15)	Digestive	Hemorrhagic colitis[b]	Hospitalization
		22 (12)	[22 hrs]	Digestive	Diarrhea[b]	Hospitalization
Durden 5310	75/M	25 (15)	29 (19)	Respiratory	Dyspnea	Hospitalization
Epstein 6299	74/M	16 (6)	27 (17)	Body as a whole	Chills	Hospitalization
		16 (6)	27 (17)	Body as a whole	Fever	Hospitalization
		21 (11)	27 (17)	Respiratory	Dyspnea	Hospitalization
Gaona 5050	41/F	2	2	Body as a whole	Accidental injury	Hospitalization
Ovetsky 5877#	56/M	3 (0)	10 (7)	Cardiovascular	Congestive heart failure	Hospitalization
		3 (0)	10 (7)	Respiratory	Respiratory disorder	Hospitalization
		4 (1)	10 (7)	Respiratory	Pneumonia	Hospitalization
Simon 5386#	60/F	3(1)	10 (8)	Respiratory	Lung disorder	Hospitalization
Simon 5478	81/F	14 (4)	27 (17)	Respiratory	Lung disorder	Hospitalization
		14 (4)	27 (17)	Body as a whole	Infection	Hospitalization
Simon 5677	49/M	24 (13)	38 (27)	Respiratory	Lung disorder	Hospitalization
		24 (13)	38 (27)	Cardiovascular	Myocardial infarct	Hospitalization
Simon 6328	60/M	19 (9)	23 (13)	Body as a whole	Infection	Hospitalization
		19 (9)	23 (13)	Respiratory	Lung disorder	Hospitalization
Patients with Serious Adverse Events in the Clarithromycin 500 mg BID Treatment Group						
Fogarty 6308#	78/M	2 (0)	3 (1)	Nervous	Confusion	Required Intervention
Handshoe 6266#	75/M	4 (0)	6 (2)	Respiratory	Respiratory disorder	Hospitalization
		7 (3)	13 (9)	Cardiovascular	Atrial fibrillation	Hospitalization
Simon 5674#	63/M	15 (9)	41 (35)	Respiratory	Lung disorder	Hospitalization
		15 (9)	22 (16)	Body as a whole	Infection	Hospitalization
Sprague 5134	77/F	15 (4)	17 (6)	Nervous	Vertigo	Hospitalization
Ulrich 5118	58/M	28 (18)	28 (18)	Cardiovascular	Heart arrest	Death
Upchurch 6523	64/F	45 (35)	49 (39)	Cardiovascular	Myocardial infarct	Hospitalization; Life-threatening
		50 (40)	51 (41)	Skin & appendages	Angioedema	Hospitalization

\# Patient prematurely discontinued from the study.
[a] Days posttreatment are presented in parentheses; if less than 1 day, duration in hours is presented in brackets; 0 = study drug discontinued as of specified day; Cont. = event continued as of specified day.
[b] Drug-relationship classified as possible, probable, or definite.

3.2.2.4.4.1.5 Deaths

According to the Applicant, two deaths were reported in the study, neither of which was considered related to study drug by the investigators.

Patient #5074 (Inv. Netzel) - An 85-year-old male assigned to the CDTR-PI 200 mg group who experienced worsening of end-stage chronic obstructive pulmonary disease 21 days after the final dose of study drug. Although other medications were prescribed, he did not respond to treatment and died on Study Day 37.

Patient #5118 (Inv. Ulrich) - A 58-year-old male assigned to the CLA group who developed chest pain at home 18 days after the final dose of study drug. The emergency squad was called; however, the patient died of cardiac arrest before they arrived.

MO Comment: ***The MO reviewed these cases and found no relation to study drug.***

3.2.2.4.4.2 Laboratory

Statistically significant treatment differences were observed among the treatment groups in mean change from baseline to post-therapy in neutrophils, alkaline phosphatase, SGPT/ALT, and LDH. The differences among the treatment groups were not considered to be clinically meaningful by the Applicant. A summary of the laboratory parameters for which statistically significant differences among treatment groups were observed in mean change from baseline to post-therapy is presented in Table 59. (Volume 317 of 322, page 129).

MO Comment: ***The MO agrees that these changes are not clinically significant.***

Table 59. Statistically Significant Differences Among Treatment Groups in Mean Change From Baseline to Post-Therapy for Laboratory Test Parameters According to the Applicant

	CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CLA 500 mg BID	
Parameter (unit)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Neutrophils (%)						
Baseline	291	64.71 (10.61)	294	66.38 (9.96)	294	65.23 (10.44)
Post-Therapy	262	62.05 (10.61)	267	60.93 (9.59)	269	61.71 (9.90)
Mean Change to Post-Therapy (p=0.046)	257	-2.96 (9.38)[&]	259	-4.99 (10.40)	261	-3.52 (9.00)
Alkaline Phosphatase (U/L)						
Baseline	294	78.60 (22.63)	295	80.12 (28.39)	301	77.64 (22.69)
Post-Therapy	268	74.91 (21.51)	262	74.48 (21.74)	273	77.45 (22.73)
Mean Change to Post-Therapy (p<0.001)	265	-3.85 (8.89)[@]	257	-4.95 (15.48)[#]	271	0.28 (9.32)
SGPT/ALT (U/L)						
Baseline	296	25.42 (18.09)	298	24.80 (18.88)	300	25.09 (22.37)
Post-Therapy	267	25.11 (17.33)	265	26.92 (19.30)	273	24.60 (15.70)
Mean Change to Post-Therapy (p=0.044)	266	-0.64 (9.11)[&]	261	2.02 (11.11)[#]	270	-0.46 (18.58)
LDH (U/L)						
Baseline	293	169.42 (33.50)	292	168.41 (41.48)	300	167.05 (42.44)
Post-Therapy	268	163.21 (32.25)	261	162.38 (37.59)	269	164.16 (37.14)
Mean Change to Post-Therapy (p=0.043)	264	-5.97 (23.15)[@]	253	-5.68 (28.89)[#]	267	-0.86 (26.65)

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin; SD = standard deviation
[&] = Statistically significant difference between CDTR-PI 200 mg and CDTR-PI 400 mg, p≤0.05.
[@] = Statistically significant difference between CDTR-PI 200 mg and CLA, p≤0.05.
[#] = Statistically significant difference between CDTR-PI 400 mg and CLA, p≤0.05.

When individual patient changes were assessed by the Applicant using shift tables for laboratory tests, the majority of the laboratory test values were found to be within normal range at both baseline and post-therapy. Statistically significant treatment differences were observed between the two CDTR-PI groups for AST (p=0.045) and ALT (p=0.03), with higher proportions of patients in the CDTR-PI 400 mg group demonstrating shifts from normal at baseline to abnormal at post-therapy in the direction of concern. Statistically significant treatment differences were observed between the CDTR-PI 400 mg and CLA groups for hemoglobin (p=0.036) and BUN (p=0.030), with higher proportions of patients in the CLA group demonstrating shifts from normal at baseline to abnormal at post-therapy in the direction of concern.

The proportions of patients with potentially clinically significant laboratory values were generally similar among the treatment groups. One patient in the CDTR-PI 400 mg group was prematurely discontinued from the study due to elevated pretreatment liver enzymes; the investigator considered the abnormal liver function test results possibly due to hepatitis and not related to study drug. Table 60. (Volume 317 of 322, page 130) presents the proportions of patients with potentially clinically significant laboratory values.

Table 60. Proportions of Patients with Potentially Clinically Significant Laboratory Values According to the Applicant

		CDTR-PI 200 mg BID		CDTR-PI 400 mg BID		CLA 500 mg BID	
Laboratory Parameter (unit)	**Potentially Clinically Significant Criteria**	**n/N**	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Hematology		**6/277**	**(2%)**	**4/287**	**(1%)**	**5/292**	**(2%)**
Hemoglobin (g/dL)	↓ from pre-therapy of 2 g/dL or more or below the normal limit if baseline value is missing	4/277	(1%)	1/287	(<1%)	3/292	(1%)
Hematocrit (%)	<37 male; <32 female	3/271	(1%)	4/286	(<1%)	3/290	(1%)
Platelet Count ($x10^3$ mcL)	<100	0/275	(0%)	0/287	(0%)	0/291	(0%)
Hepatic Chemistry		**1/280**	**(<1%)**	**1/286**	**(<1%)**	**2/293**	**(1%)**
Total Bilirubin (mg/dL)	NL, Low, Missing BL: >2.0 High BL: >2.5	0/280	(0%)	1/286	(<1%)	0/293	(0%)
AST (U/L)		1/280	(<1%)	0/286	(0%)	2/293	(1%)
	NL, Low, Missing BL: ≥2xULN	1/280	(<1%)	0/286	(0%)	2/293	(1%)
	≥3xULN	1/280	(<1%)	0/286	(0%)	1/293	(<1%)
	≥5xULN	1/280	(<1%)	0/286	(0%)	0/293	(0%)
	High BL: ≥3xBL	0/280	(0%)	0/286	(0%)	0/293	(0%)
ALT (U/L)		1/280	(<1%)	0/286	(0%)	1/293	(<1%)
	NL, Low, Missing BL: ≥2xULN	1/280	(<1%)	0/286	(0%)	1/293	(<1%)
	≥3xULN	1/280	(<1%)	0/286	(0%)	0/293	(0%)
	≥5xULN	1/280	(<1%)	0/286	(0%)	0/293	(0%)
	High BL: ≥3xBL	0/280	(0%)	0/286	(0%)	0/293	(0%)
Metabolic/Nutritional Chemistry		**0/280**	**(0%)**	**0/285**	**(0%)**	**0/291**	**(0%)**
Glucose (mg/dL)	<45	0/280	(0%)	0/285	(0%)	0/291	(0%)
Renal Chemistry		**2/283**	**(1%)**	**1/287**	**(<1%)**	**6/293**	**(2%)**
BUN (mg/dL)	>30	2/283	(1%)	1/287	(<1%)	6/293	(2%)
Creatinine (mg/dL)	NL, Low, Missing BL: >2.0 High BL: >2.5	0/283	(0%)	0/287	(0%)	2/293	(1%)

CDTR-PI = cefditoren pivoxil; CLA = clarithromycin;
BL = baseline; NL = normal; ULN = upper limit of normal range

3.2.2.4.4.3 Vital Signs

No clinically significant differences were observed among the treatment groups in mean change from baseline to post-therapy or follow-up.

3.2.2.5 Reviewer's Comments/Conclusions

3.2.2.5.1 Efficacy

The efficacy results of CEF97-005 do not support the use of cefditoren-pivoxil 200 mg PO BID for the treatment of AECB. If a delta of 10% is required, the Applicant's data analyses (when adjusted for multiple comparisons) suggest that CDTR-PI 200 mg [97.5% CI –10.9, 5.6] and CDTR-PI 400 mg [97.5% CI –13.8, 3.2] are not equivalent to CLA 500 mg in the clinically evaluable population at Follow-Up. If a delta of 15% is used then both doses would be considered equivalent based on the Applicant's data (when adjusted for multiple comparisons). However, the MO disagrees with the evaluability and outcome criteria defined by the Applicant and used by the Applicant in their analyses. Based on the MO's reanalysis neither CDTR-PI 400 mg [97.5% CI –

24.7, 1.5] nor CDTR-PI 200 mg [97.5% CI –16.8, 9.1] appears to be equivalent to CLA 500 mg in the evaluable population at Follow-Up.

If a delta of 10% is required, the Applicant's data analyses (when adjusted for multiple comparisons) suggest that neither CDTR-PI 200 mg [97.5% CI –10.2, 9.3] nor CDTR-PI 400 mg [97.5% CI –14.0, 15.9] are equivalent to CLA 500 mg in the microbiologically evaluable population at Follow-Up. If a delta of 15% is used then both doses would be considered equivalent based on the Applicant's data (when adjusted for multiple comparisons). However, the MO disagrees with the evaluability and outcome criteria defined by the Applicant and used by the Applicant in their analyses. Based on the MO's reanalysis, CDTR-PI 400 mg is not equivalent to CLA 500 mg [97.5% CI -19.8, 6.7]; however, CDTR-PI 200 mg appears to be equivalent to CLA 500 mg [97.5% CI –9.6, 16.2] in the microbiologically evaluable population at Follow-Up.

The trend toward better outcomes in the CDTR-PI 200 mg group versus the CDTR-PI 400 mg group is worrisome and is not adequately explained by differences in baseline demographics, compliance, or discontinuations due to AEs between the groups.

Of interest the cure rates at Follow-Up determined using the stricter criteria defined by the MO approach those that might be expected for placebo, raising the fundamental issue of the utility of the use of antimicrobials for the treatment of AECB.

3.2.3.1.3 Safety

The number of adverse events and drug-related adverse events, during therapy was significantly higher in the CLA group than the CDTR-PI 200 mg group. The number of serious adverse events and withdrawals from the study due to adverse events during treatment are similar across all treatment arms. Diarrhea and vaginal moniliasis were reported significantly more often for the CDTR-PI 400 mg group in the all and treatment related analyses. Not unexpectedly, taste perversion was reported more significantly often for the CLA group in the all and treatment related analyses. Changes in laboratory findings and vital signs were consistent between treatment arms.

Statistical Reviewer's Comments and Conclusions:

Efficacy Results:

Based on the reanalysis of the Applicant's data by applying the medical officer's evaluability and outcome criteria at follow-up in the evaluable population, neither CDTR-PI 200 mg (97.5% CI: -24.7, 1.5) nor CDTR-PI 400mg (97.5% CI: -16.8, 9.1) appears to be equivalent to the approved

comparator CLA 500 mg BID, using a delta of 10% (table 46). Based on these results, we conclude that the efficacy results of CEF97-005 do not support the use of CDTR-PI 200 mg PO BID for the treatment of AECB.

3.2.3 Overall Conclusion and Recommendation

The Applicant has not provided adequate evidence that cefditoren-pivoxil 200 mg PO BID x 10 days is efficacious in the treatment of acute bacterial exacerbation of chronic bronchitis, therefore this dose of cefditoren-pivoxil should not be approved for this indication. Cefditoren-pivoxil appears generally safe; however, based on the Medical Officer's efficacy analyses, the Applicant has failed to provide data supporting its efficacy when compared to an approved comparator.

Study CEF97-003 represents an underpowered study due to the loss of patients from questionable investigators and due to stricter evaluability and outcome criteria imposed by the MO. It is adequate, however, to serve as a supporting study to another that shows equivalence of CDTR-PI 400 mg PO BID x 10 days to an approved comparator.

Study CEF97-005 remains adequately powered even after the loss of patients from questionable investigators and with the stricter evaluability and outcome criteria imposed by the MO. However, based on the MO's analyses of data it does not show equivalence of either CDTR-PI 200 mg or CDTR-PI 400 mg to an approved comparator. In addition, the lack of a dose response between the CDTR-PI 200 mg group and CDTR-PI 400 mg group is unexplained and contrary to the outcome expected based on PK and MIC data. It is also contrary to the finding in study CEF97-003, which suggested that CDTR-PI 200 mg is inferior to CDTR 400 mg for the treatment of AECB.

The MO and the Statistician recommend the Applicant perform an additional statistically adequate and well controlled study comparing cefditoren-pivoxil 400 mg PO BID x 10 days to an approved comparator, if they wish to further pursue this indication.

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